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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/751,072	01/02/2004	Sven Eyckerman	2676-6264US	2266
24247	7590	03/09/2009		
TRASKBRITT, P.C. P.O. BOX 2550 SALT LAKE CITY, UT 84110			EXAMINER HOWARD, ZACHARY C	
			ART UNIT 1646	PAPER NUMBER
			NOTIFICATION DATE 03/09/2009	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTOMail@traskbritt.com

Office Action Summary

Application No.

10/751,072

Applicant(s)

EYCKERMAN ET AL.

Examiner

ZACHARY C. HOWARD

Art Unit

1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 January 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 3, 11, 13, 16 and 31 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 3, 11, 13, 16 and 31 is/are rejected.
- 7) ☒ Claim(s) 1 and 31 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 22 January 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 1/12/2009
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 1/12/09 has been entered.

Status of Application, Amendments and/or Claims

The amendment of 1/12/08 has been entered in full. Claims 27-30 are canceled. Claims 1, 3, 11, 13, 16 and 31 are pending and are under consideration.

Information Disclosure Statement

The Information Disclosure Statement of 1/12/2009 has been fully considered.

Withdrawn Objections and/or Rejections

All rejections of claims 27-30 are moot in view of the cancellation of said claims.

Maintained Objections and/or Rejections

Claim Rejections – 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3, 11, 13 and 16 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Eyckerman et al (1999. Eur Cytokine Netw. 10(4): 549-546; cited on the 11/22/02 IDS). This rejection was set forth previously and maintained at pg 3-10 of the 11/10/08 Office Action.

Applicants' arguments (1/12/09; pg 4-5) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that Eyckerman et al (1999) do not teach each and every element of the claims; specifically, they do not teach a bait polypeptide because the myc-tag taught therein is not equivalent to a bait polypeptide (pg 4). Applicants argue that "for one of ordinary skill in the art, a clear distinction exists between a tag, such as a myc-tag, and a bait; the tag being a short peptide of only a few amino acids, intended as a marker, whereas a bait is a longer oligopeptide that forms a normal part of a protein-protein interaction in a cellular system" (pg 5). Applicants submit that Van Crielinge (1999) teaches at page 10 that "at least one commonly used two-hybrid vector contains an epitope tag (HA) that is preferably introduced in frame with the target/bait" and "another commonly used two-hybrid vector [has] an HA tag". Applicants argue that "the art identifies two-hybrid constructs comprising both a bait and a tag, each being referred to by their separate functions without any conflation of the two epitopes" (pg 5).

Applicants' arguments have been fully considered but are not found persuasive. While Van Crielinge teaches that fusion polypeptides comprising a bait polypeptide can also include an HA epitope tag (fused in-frame between the GAL4 DNA-binding domain and the bait polypeptide), Van Crielinge also teaches fusion polypeptides comprising a bait polypeptide without an HA epitope tag (pg 9). Furthermore, Van Crielinge describes a "bait" polypeptide only as "a protein of interest" (pg 4); this description does not exclude an epitope tag from being used as such "bait" proteins. Furthermore, while Applicants argue a size distinction between an epitope tag (e.g., myc) and a bait polypeptide, Van Crielinge does not teach such a distinction, or any size limitation for the bait polypeptide. "Short" peptides have been used in the relevant art as bait in a

yeast two-hybrid screen. For example, Clayberger et al (U.S. Patent 5,935,797; published 8/10/99) teaches use of a 15 amino acid bait in a two-hybrid screen: "pXL-17 was created as the bait plasmid in the yeast two hybrid screen ... In pXL-17, the peptide DQ65-79 was fused to the carboxyl terminal end of the yeast GAL4 DNA binding domain (GAL4-BD)" (col 9, lines 22-26). The myc tag itself has been used as such bait; for example, Fujiwara et al (2002. *Biochemistry*. 41(42): 12729-38) teaches a bait-prey system wherein the bait comprised a single or five copies of the myc epitope tag (pg 12733). Furthermore, the relevant art has also used fragments of the myc protein comprising the myc epitope tag as bait in two-hybrid screening. The myc epitope tag is located in the C-terminal region of the protein between amino acids 408-439 (pg 2 of Hilpert et al, 2001. *Protein Engineering*. 14(10): 803-806; 11 pages as printed). Estojak et al (1995. *Molecular and Cellular Biology*. 15(10): 5820-5829) teaches a bait molecule wherein "pLexA-Myc expresses the carboxy terminal 176 amino acids of human c-Myc" (pg 5821). Bao et al (1996. *Oncogene*. 12: 2171-2176) teaches an interaction trap wherein "[t]he Lex-C-myc bait contains the carboxy-terminal 176 amino acids of human C-myc" (pg 2175). Bannasch et al (1999. *Oncogene*. 18: 6810-6817) teach a bait construct encoding a fusion protein of Gal4 DNA binding domain (Gal4 BD) and "the central and C-terminal portion of the Myc protein (aa 180-436) (MYC-CT)" (pg 6811). Junqueira et al (2003. *Oncogene*. 22: 2772-2781) teach "Myc282-437 bait lacking the last three amino acids" (pg 2773). Finally, the two-hybrid assay taught by Van Criekeing is not the only prior art which informs the "bait" terminology used in the instant claims. The instantly claimed "receptor-interaction trap" is significantly different in structure from the two-hybrid assay described by Van Criekeing. In the instant "trap" the bait is fused to a membrane-spanning receptor rather than to a DNA-binding portion of transcription factor as in the "standard" two-hybrid assay taught by Van Criekeing. Other variants of the two-hybrid assay are taught by the prior art; for example, Zhang et al (2000. *Nature Biotechnology*. 18: 71-74) teaches that "[t]he repressor reconstitution assay we used to isolate peptide-binding peptides is one of many variants of the two-hybrid concept" (page 73). Zhang does not use the term "bait", however, the skilled artisan would recognize that the "target peptide" used in Figure 1 is analogous to the "bait"

polypeptide (the "library encoded peptide" being analogous to a "prey" peptide). Zhang teaches that the target peptide is "an epitope of 13-14 amino acids" and is fused to a DNA-binding domain. Therefore, the prior art appreciates that bait polypeptides can be short peptides including epitopes.

Furthermore, the specification is silent as to any size constraint on the bait polypeptide, and defines a "heterologous bait polypeptide" only as "a polypeptide comprised in the cytoplasmic domain of a receptor, and indicates that the polypeptide is within the cytoplasmic domain, or fused to the cytoplasmic domain; there is another polypeptide that is not present in the cytoplasmic domain of the non-recombinant receptor" and that the term "[b]ait" as used herein means that this polypeptide can interact with other polypeptides not belonging to the normal receptor complex" (§ 64, pg 15). This definition provides no limitation on the size of the "heterologous bait polypeptide". Nothing in this definition excludes peptides or other small polypeptides. Thus, nothing in this definition excludes the heterologous myc tag found in the receptor taught by Eyckerman.

In summary, it is maintained that the "myc tag" as taught by Eyckerman et al is encompassed by the term "bait" used in the instant claims. Therefore, the rejection is maintained herein for the reasons set forth previously.

New Objections and/or Rejections

Claim Objections

Claims 1 and 31 are objected to because of the following informalities:

(1) In claim 1, line 7, the phrase "JAK-binding site" is missing an article (e.g., "a JAK-binding site").

(2) Claim 31 does not end with a period.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 recites the limitation "JAK-binding site" in lines 6-7. There is insufficient antecedent basis for this limitation in the claim. Specifically, lines 6-7 recite "a heterologous bait polypeptide heterologous to the domain derived from a cytoplasmic domain of a mammalian receptor and JAK-binding site". Thus, it appears that the bait polypeptide is heterologous to the domain and to the JAK-binding site. However, nowhere else does the recited receptor include a JAK-binding site. Thus, the recitation that the bait polypeptide is heterologous to the JAK-binding site lacks antecedent basis in the claim. For purposes of prosecution the claim will be interpreted as encompassing a receptor comprising a JAK-binding site (because in order for the bait to be heterologous to the JAK-binding site, the receptor must include a JAK-binding site).

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 31 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a recombinant receptor comprising: an extracellular ligand-binding domain of a mammalian receptor; a cytoplasmic domain comprising a domain derived from a cytoplasmic domain of a mammalian receptor, and at least one activation site that is a tyrosine residue, and a heterologous bait polypeptide heterologous to the domain derived from a cytoplasmic domain of a mammalian receptor; wherein said cytoplasmic domain comprises a JAK-binding site; and wherein the activation of said recombinant receptor is inhibited by binding of a fusion protein to said bait polypeptide, said fusion

protein comprising a prey polypeptide and an inhibitor of the activation of said recombinant receptor that is selected from the group consisting of a member of the SOCS family, a JAK-phosphatase, and a STAT-phosphatase, and does not reasonably provide enablement for

a recombinant receptor comprising: an extracellular ligand-binding domain of a mammalian receptor; a cytoplasmic domain comprising a domain derived from a cytoplasmic domain of a mammalian receptor, at least one activation site that is a tyrosine residue, and a bait polypeptide heterologous to the domain derived from a cytoplasmic domain of a mammalian receptor and JAK binding site. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 31 has been newly presented in the claim amendments filed 1/12/2008. Claim 31 is an independent claim that differs significantly from independent claim 1 in the following manner. First, claim 31 is indefinite for the reasons set forth above in the section titled "Claim Rejections - 35 USC 112 2nd, paragraph". However, for purposes of prosecution the claim has been interpreted as encompassing a receptor comprising a JAK-binding site, as in claim 1. Second, claim 31 lacks the functional limitation that is present in claim 1; i.e., "wherein the activation of said recombinant receptor is inhibited by binding of a fusion protein to said heterologous bait polypeptide, said fusion protein comprising a prey polypeptide and at least one of an inhibitor of the activation of said recombinant receptor and a recruitment site for the inhibitor of the activation of said recombinant receptor". Thus, claim 31 encompasses a genus of variant receptors that are defined by structure alone and are not required to have any particular functionality required for using the receptors as disclosed in the specification.

The nature of the invention is a recombinant receptor for use in screening for a molecule that disrupts an interaction between a bait and a prey molecule. The claimed receptor comprises a ligand-binding extracellular domain (ECD) from a mammalian receptor and a cytoplasmic domain with at least three parts: (1) a cytoplasmic domain from a mammalian receptor; (2) at least one activation site that is a tyrosine residue and

(2) a heterologous bait polypeptide; furthermore, the cytoplasmic domain has been interpreted as comprising "a JAK binding site".

The specification provides limited teachings regarding the nature of the receptor from which the cytoplasmic domain is derived. The only specific receptor cytoplasmic domain that is disclosed in the specification is derived from the leptin receptor. The specification teaches "a homomultimerizing recombinant leptin receptor with a heterologous bait polypeptide fused into or, preferentially, at the carboxyterminal end of its cytoplasmic domain" (pg 5, ¶ [0014]). The specification does not teach any other specific receptor cytoplasmic domains that can be used in the claimed recombinant receptor. Furthermore, all of the working examples in the specification that are directed to a recombinant receptor encompassed by the claims include a very specific derivative of the cytoplasmic domain of the leptin receptor. This derivative is designated LepRFFY (see pg 18, ¶ [0079] and pg 22, ¶ [0093]) and includes a leptin receptor cytoplasmic domain with a phenylalanine residue at position 985; a phenylalanine residue at position 1077; and a tyrosine residue at position 1138. Example 1 (pg 22) describes the "specific inhibition of activation of the EpoR-LepRFFY-EpoR by the SOCS3-CISSH2 chimera is disrupted by overexpression of SOCS2" (pg 22, ¶ [0093]). In the recombinant receptor used in this example (EpoR-LepRFFY-EpoR), the first EpoR is the extracellular ligand-binding domain; the LepRFFY is the cytoplasmic domain from a receptor including an activation site (the 'Y' that is residue 1138 in native LepR) and the second EpoR is the bait molecule. The SOCS3-CISSH2 is a fusion protein consisting of a CIS protein in which the SH2 domain of CIS (amino acids 82-218) is replaced with the SH2 domain of SOCS (amino acid residues 46-184; see pg 20, ¶ [0084]). The CIS portion is the binding partner (prey) for the bait molecule (the second EpoR) and the SOCS3 SH2 domain is an inhibitor of activation of the receptor. As taught in Eyckerman et al (2005), the LepRFFY "contains a functional Y1138 STAT3 recruitment motif and is therefore signaling-competent, but it lacks the Y985 and Y1077 motifs required for recruitment of negative regulators" (pg 428 of Eyckerman et al, 2005. *Nature Methods*. 2(6): 427-433; cited previously). Example 1 further teaches that the recombinant receptor shows "very strong inhibition upon co-transfection of the chimeric SOCS3 CISSH2 protein. The SH2

domain targets the SOCS3 inhibitory regions towards the activated complex, resulting in specific inhibition" (pg 23, ¶ [00100]). Example 2 does not directly relate to the claimed receptor; instead it describes use of a recombinant receptor that is not encompassed by the claims to demonstrate that a specific bait-prey (ALK4-FKB12) interaction can be disrupted by the molecule FK506. In Example 3, ALK5 and FKB12 are used as bait and prey in the recombinant receptor and fusion protein from Example 1; in addition, a PTP-1B phosphatase domain is substituted for the inhibitory SOCS3 domain in the fusion protein. The specification further teaches that the inhibitor can be a "Suppressor of Cytokine Signalling (SOCS)" family member such as SOCS1 or SOCS3 (pg 7, ¶ [0018]). The specification further teaches that the inhibitor can be a "STAT phosphatase" or a "Protein Inhibitor of Activated STAT (PIAS), preferably PIAS3" (pg 7, ¶ [0019]).

In view of the teachings of the specification, the invention appears based on the following working model. Interaction between the bait molecule (part of the recombinant receptor) and the prey molecule (part of a fusion protein) allows the inhibitory molecule (also part of said fusion protein) to inhibit the activation site (1138Y) found in the cytoplasmic domain of the recombinant receptor. This inhibition occurs even if a ligand (e.g., Epo) binds to an extracellular ligand-bind domain (e.g., EpoR) of the recombinant receptor. However, if a second molecule is added (in addition to the ligand) that disrupts the bait-prey interaction, activation occurs because the inhibitory molecule is no longer recruited to the receptor to inhibit activation at the 1138Y residue (which functions as recruitment site for a STAT3 signaling molecule). The specification does not provide any teachings regarding specific receptors other than the leptin receptor, or any specific activation sites found in other receptors, that can be used in the recombinant receptor of the invention.

While the specification does not describe any specific receptors with "a JAK binding site" other than the leptin receptor, the specification does teach a generic receptor with a cytoplasmic domain that comprises "a JAK binding site" (pg 5). Furthermore, the leptin receptor cytoplasmic domain is representative of a genus receptor cytoplasmic domains comprising JAK-binding sites that were well known in the art at the time of filing. For example, the reference Ihle et al (1995; cited previously)

teaches that "mutational analysis of receptors that contain a single chain have shown that the cytoplasmic membrane-proximal region, which contains the box 1 and box 2 motifs, is required for receptor function. Both in vitro and in vivo studies show that this region is required for association of Jaks with cytokine receptors" (pg 70). Ihle et al further describe the genus of cytokine receptors comprising such JAK binding sites (see Figure 1 and pg 70). More recent relevant art also teaches, "Jaks associate with the membrane-proximal region of cytokine receptors. Amongst receptors, there is little homology except for short stretches called the box1 region, a proline-rich motif of eight amino acids, and the box2 region, a cluster of hydrophobic amino acid residues often followed by charged amino acids" (pg 1540 of Haan et al, 2006. *Biochemical Pharmacology*. 72: 1538-1546; cited previously). In view of the teachings of the art at the time of filing, and as supported by post-filing date art, the specification at the time of filing provides enablement for a genus of "JAK binding sites" to be used in the claimed receptor (i.e., a genus of JAK-binding sites, each derived from a different cytokine receptor).

However, the claimed recombinant receptor, while comprising "a JAK binding site", is not limited to naturally occurring cytokine receptor domains that include both a JAK binding site and an activation site that is a tyrosine residue that is phosphorylated upon activation. Instead, the claims encompass a vast genus of mammalian receptor cytoplasmic domains, including both cytokine receptors and structurally unrelated receptors (e.g., nuclear hormone receptors or G-protein coupled receptors (GPCRs)) that include natural or artificial tyrosine activation sites and/or JAK binding sites.

The functionality of the receptor in screening for compounds that disrupt bait-prey interactions requires that receptor have a particular functional characteristic: that activation of the receptor is inhibited by the binding of particular prey molecules. The instant specification suggests that a variety of inhibitors can be used in the fusion protein comprising a prey molecule and an inhibitor of activation, but the relevant art teaches unpredictability as to which inhibitors will actually function as inhibitors when used with a recombinant receptor comprising the LepRFFY cytoplasmic domain and a specific bait-prey combination. The instant specification demonstrates use of a fusion

protein comprising a CIS protein in which the SH2 domain of CIS (amino acids 82-218) is replaced with the SH2 domain of SOCS3 (amino acid residues 46-184). This fusion protein was used to inhibit a recombinant receptor comprising LepRFFY as the cytoplasmic domain and EpoR residues 370-453 as the bait molecule; the CIS prey molecule binds to the EpoR bait molecule and allows the SOCS3 domain to inhibit LepRFFY activation. In view of this result, the specification suggests that the SOCS3 domain can be used as an inhibitor with any recombinant receptor. However, the relevant art shows that when a different bait-prey combination is used (FKBP12 and ALK4), many potential inhibitors fail to work. Specifically, Eyckerman et al (2005; cited previously) teaches, "we generated fusion constructs of both FKBP12 and ALK4 with a variety of inhibitory domains derived from SOCS molecules, tyrosine phosphatases and PIAS molecules. All efforts with SOCS-based i-prey constructs proved unsuccessful. Inhibition via the kinase inhibitory regions of SOCS-1 and SOCS-3 may require a very specific context or orientation of these domains. Fusion constructs with PIAS3 also did not have any inhibitory activity. In contrast, chimeric constructs containing the phosphatase domains of PTP-1B and TC-PTP (but not of SHP-1 or SHP-2) caused a substantial, specific reduction in signaling" (pg 429-430). Eyckerman further teaches that the phosphatase domain of PTP-1B works as inhibitor using a bait-prey combination that is MDM2-p53. However, another tyrosine phosphatase, TC-PTP, did not work with this combination of bait and prey. These teachings demonstrate that some inoperative embodiments will be found among the genus of receptors comprising a tyrosine activation site and a JAK-binding site and that functionally interact with the disclosed inhibitors (SOCS family members, JAK phosphatases and STAT phosphatases). This points to the even greater level of difficulty in predicting and testing which other inhibitors will work in the claimed invention in conjunction with receptors comprising a tyrosine activation site and a JAK-binding site.

The only specific inhibitors that are described in the specification are those that function in conjunction with the JAK kinase-tyrosine phosphorylation mechanism (specifically, SOCS family members, JAK phosphatases and STAT phosphatases). However, without a functional limitation in the claims, the claim encompass a vast

genus of structurally diverse receptors that would be predicted to require inhibition by other inhibitors. In view of the limited teachings of the specification and the prior art, the specification merely invites the skilled artisan to experiment in order to find inhibitors other than SOCS family members, JAK phosphatases and STAT phosphatases, such that the claimed receptor will be functionally usable by said artisan.

The teaching of a single type of activation site (tyrosine residue), and a limited genus of inhibitors that are specific to said activation site, that can be used in the claimed receptor is not sufficient to enable the vast genus of potential engineered cytoplasmic domains that are encompassed by the claimed receptor. Due to the large quantity of experimentation necessary to (1) generate the large number of (a) recombinant receptors comprising tyrosine activation sites and JAK binding sites and (b) potential prey-inhibitor fusion molecules and (2) test such combinations for functionality (inhibition of receptor activity) in a method of screening, the lack of direction/guidance presented in the specification regarding other inhibitors that will work in conjunction with a receptor comprising a tyrosine activation site and a JAK-binding site, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claim 31 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicants are claiming and what Applicants have possession of.

Claim 31 has been newly presented in the claim amendments filed 1/12/2008. Claim 31 is an independent claim that differs significantly from independent claim 1 in the following manner. First, claim 31 is indefinite for the reasons set forth above in the section titled "Claim Rejections - 35 USC 112 2nd", paragraph". However, for purposes of prosecution the claim has been interpreted as encompassing a receptor comprising a JAK-binding site, as in claim 1. Second, claim 31 lacks the functional limitation that is present in claim 1; i.e., "wherein the activation of said recombinant receptor is inhibited by binding of a fusion protein to said heterologous bait polypeptide, said fusion protein comprising a prey polypeptide and at least one of an inhibitor of the activation of said recombinant receptor and a recruitment site for the inhibitor of the activation of said recombinant receptor". Thus, claim 31 encompasses a genus of variant receptors that are defined by structure alone and are not required to have any particular functionality required for using the receptors as disclosed in the specification.

The claims are genus claims because the claims are directed to variant recombinant receptors. Each genus is highly variant because a significant number of structural differences between genus members are permitted. In particular, claim 31 encompasses a receptor comprising a cytoplasmic domain derived from any type of receptor with at least one tyrosine activation site and a JAK binding site. As such, these claims encompass cytoplasmic domains from a vast array of structurally different receptors, including single transmembrane cytokine receptors (including mutated variants) as well as receptors without transmembrane domains (e.g., nuclear hormone receptors) or multiple transmembrane domains (e.g., G-protein coupled receptors), any of which could be artificially engineered to include a tyrosine activation site and a JAK binding site. The only structural limitation of the cytoplasmic domain of the claimed receptor is that it must comprise a tyrosine activation site and a JAK-binding site.

The combination of the teachings in the specification and the prior art at the time of filing (described above in the enablement rejection), indicate support for possession of a genus of recombinant receptors comprising a cytoplasmic domain derived from a cytokine receptor comprising a JAK-binding site and a tyrosine activation site, wherein said activation site can be inhibited by a prey molecule comprising an inhibitor of such

activation sites (SOCS family member, JAK phosphatase and STAT phosphatases). However, claim 31 encompasses structurally different receptors comprising a tyrosine activation site and a JAK binding site, but that are not required to be functionally inhibited by a prey molecule comprising SOCS family member, JAK phosphatase and STAT phosphatases. Such a genus includes variants that are not capable of inhibition by any inhibitor, or that that can be inhibited by structurally and/or functionally different inhibitors. The limited description in the specification does not indicate that Applicants had possession of the full range of such a genus at the time of filing.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of recombinant receptors. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed by the claims. Thus, no identifying characteristics or properties of the instant receptors are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. The skilled artisan would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed" (pg 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (pg 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only: a recombinant receptor comprising: an extracellular ligand-binding domain of a mammalian receptor; a cytoplasmic domain comprising a domain derived from a cytoplasmic domain of a mammalian receptor, and at least one activation site that is a tyrosine residue, and a heterologous bait polypeptide heterologous to the domain derived from a cytoplasmic domain of a mammalian receptor; wherein said cytoplasmic domain comprises a JAK-binding site; and wherein the activation of said recombinant receptor is inhibited by binding of a fusion protein to said bait polypeptide, said fusion protein comprising a prey polypeptide and an inhibitor of the activation of said recombinant receptor that is selected from the group consisting of a member of the SOCS family, a JAK-phosphatase, and a STAT-phosphatase, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicants are reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (pg 1115).

Claim Rejections – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 31 is rejected under 35 U.S.C. 102(b) as anticipated by Eyckerman et al, 1999 (Eur Cytokine Netw. 10(4): 549-546; cited previously).

New claim 31 is directed to a recombinant receptor comprising: an extracellular ligand-binding domain of a mammalian receptor; a cytoplasmic domain comprising a domain derived from a cytoplasmic domain of a mammalian receptor, at least one activation site that is a tyrosine residue, and a bait polypeptide heterologous to the domain derived from a cytoplasmic domain of a mammalian receptor and JAK binding site. Claim 31 is indefinite for the reasons set forth above in the section titled "Claim Rejections - 35 USC 112 2nd, 2nd paragraph". However, for purposes of prosecution the claim has been interpreted as encompassing a receptor comprising a JAK-binding site (because in order for the bait to be heterologous to the JAK-binding site, the receptor must include a JAK-binding site).

Eyckerman teaches recombinant receptors comprising the mouse leptin receptor with one or more tyrosine residue mutations in the cytoplasmic domain and a heterologous myc-tag polypeptide (pg 550, column 1; eight different receptors are disclosed each with different mutations). Eyckerman teaches that Tyr1138 is an activation site required for signaling in response to leptin binding ("Tyr to Phe mutations in the cytoplasmic tail of the mouse leptin receptor confirmed the critical role of Tyr1138 (a YxxQ motif) and STAT-3 activation for induction of leptin-induced genes in PC12"; see Abstract, pg 549). One of the mutant receptors taught by Eyckerman comprises two tyrosine mutations (Tyr985Phe and Tyr1077Phe) but retains the Tyr1138 activation site (pg 550). This is the same combination of mutations (Tyr985Phe and Tyr1077Phe) and wild type tyrosine (Tyr1138) as used in the LepRFFY receptor described in Example 1 of the instant application (see Figure 1). This receptor meets all of the structural

requirements of claim 31: "an extracellular ligand binding domain of a mammalian receptor" (e.g., mouse leptin receptor domain); a cytoplasmic domain comprising a domain derived from a cytoplasmic domain of a mammalian receptor (e.g., leptin receptor domain), at least one activation site that is a tyrosine residue (e.g., Tyr1138) and a heterologous bait polypeptide (e.g., the myc-tag), and wherein the cytoplasmic domain comprises a JAK binding site (Eyckerman teaches on page 549 that the leptin receptor includes a "a JAK tyrosine kinase binding site (Box 1)").

Therefore, the teachings of Eyckerman et al anticipate claim 31.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

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